REMARKS

Claims 4 and 27-32 are currently pending. Claims 4, 27, and 28 are amended herein to clarify the claimed subject matter. New claim 33 is presented herein. Accordingly, instant claims 4 and 27-33 are under consideration.

Any amendment, however, is not to be construed as abandonment of any subject matter of the originally filed application. Accordingly, it is to be understood that Applicant reserves the right to reintroduce subject matter deleted from the application by the foregoing amendments and to file one or more divisional, continuation, and/or continuation in part applications directed to such subject matter.

Support for amendment to the claims is found throughout the specification and in the original claims. More specifically, support for amendment to claim 4 is found, for example, at page 16, line 29 through page 17, line 2, wherein support for comparing the first and second rounds of sequencing of each immobilized single-stranded template nucleic acid molecule to confirm sequencing data is found. Support for amendment to claim 27 is found, for example, in original claim 4. Support for amendment to claim 28 is found, for example, in original claim 27. No issue of new matter is introduced by these amendments.

Support for new claim 33 is found throughout the specification and in the original claims. More specifically, support for new claim 33 is found in original claim 4 and at page 17, lines 7-8. No issue of new matter is introduced by this amendment.

Applicant is submitting herewith a Substitute Sequence Listing to correct a clerical error identified in the nucleic acid sequence designated therein as SEQ ID NO: 15 and to add SEQ ID NO: 16, the restriction site for BsaBI, which is included in Table 2 of the specification, but was inadvertently not included in the previously filed Sequence Listing. More specifically, the sequence shown at page 24, line 26 of the specification as filed is GAGTCNTGGCCANNNN. The previous amendment to the specification to include a sequence identifier, namely SEQ ID NO: 15, incorrectly listed the sequence as GAGTCNTGGNNNN, thereby omitting the CCA nucleotides at positions 10-12 of the sequence presented at page 24, line 26 of the specification.

The present amendments to the specification and Substitute Sequence Listing are rendered to rectify the clerical error that led to the omission of these nucleotides. Support for the amendments included in the Substitute Sequence Listing is found, for example, at page 24, line 26 and in Table 2 of the specification. No issue of new matter is hereby introduced.

A paper copy and computer readable format (CRF) copy of the Substitute Sequence Listing are attached hereto, along with a separate Amendment directing their entry into the record, and a statement that the content of the paper and CRF copies are the same and include no new matter.

Claim Objections

Claim 28 is objected to because it depends from itself. Claim 28 is amended herein to correct this clerical error and instant claim 28 depends from claim 27. It is, therefore, believed that the objection to this claim is obviated.

Rejections under 35 U.S.C. § 112

Claims 4 and 27-32 are rejected under 35 U.S.C. § 112, second paragraph, for alleged indefiniteness. Claim 4 is amended herein to delete the allegedly indefinite subject matter. Claim 4 is also amended herein include a step of comparing the first and second rounds of sequencing of each single-stranded template nucleic acid molecule so as to confirm sequencing data. In view of the amendments to the claims, the rejection, as it applied to claims 4 and 27-32 is obviated.

Claims 27 and 28 are amended herein to delete the allegedly indefinite subject matter. Accordingly, it is believed that the rejection is obviated by these amendments.

In view of the amendments to the claims, Applicant respectfully requests reconsideration and withdrawal of the rejection of the claims under 35 USC § 112, second paragraph.

Rejections under 35 USC § 103

Claims 4, 27-29, and 30-31 are rejected under § 103(a) as allegedly unpatentable over Balasubramanism [*sic*], which clearly should read Balasubramanian et al. (WO 01/57248; published 9/2001) as evidenced by Cheeseman [United States Patent Number (USPN) 5,302,509; issued 1994] and in view of Lackey et al. (USPN 5,652,126). In view of the clarifying amendments to the claims and arguments presented herein, this rejection is respectfully traversed.

Claim 4 is amended herein to clarify that the claimed method is directed to sequencing a nucleic acid, the method comprising: (a) forming an array of immobilised single-stranded template nucleic acid molecules wherein the density of immobilised single-stranded template nucleic acid molecules is 10^6-10^9 different template sequences per cm^2; (b)determining the sequences of the immobilised single-stranded template nucleic acid molecules by synthesising a complementary copy of the template sequences, thereby performing a first round of sequencing; (c) removing the complementary copy of the template sequence; (d) performing a second round of sequencing of the immobilised single-stranded template nucleic acid molecules, and (e) comparing the first and second rounds of sequencing of each immobilized single-stranded template nucleic acid molecule to confirm sequencing data.

Accordingly, the instantly claimed invention differs from the combined teachings of Balasubramanian et al., Cheeseman, and Lackey et al. in at least one significant respect. In short, none of the cited references alone or in combination teaches a method wherein the sequences of immobilised single-stranded template nucleic acid molecules are determined by performing a first round of sequencing and then resequenced in a second round of sequencing, and data from the first and second rounds of sequencing of each immobilized single-stranded template nucleic acid molecule are compared to confirm the sequencing data results. The present method, thereby, provides a novel and non-obvious combination of steps that reduces sequencing errors that may arise from methods that call for a single cycle of sequencing.

Indeed, the Examiner acknowledges that, with respect to claim 4, Balasubramanian et al. do not teach a method further comprising removing the complementary nucleic acid strand and

performing a second round of sequencing. The Examiner also recognizes that, with respect to claim 29, Balasubramanian et al. do not teach that the primer has a recognition site for a restriction endonuclease.

The Examiner relies on Lackey et al. for allegedly teaching a method that comprises synthesizing a complementary copy nucleic acid sequence using a template sequence. In a particular embodiment wherein a DNA primer/template with a single 3' ribonucleotide is used, the Examiner maintains that cleavage at the ribonucleotide residue, followed by separation and purification of the oligonucleotide product, results in a fully regenerated and reusable primer/template. What the Examiner has apparently failed to appreciate is that there is no motivation to combine the teachings of Balasubramanian et al., Cheeseman, and Lackey et al. to allegedly arrive at the present invention. As stated in Applicant's previously presented arguments, which the Examiner failed to address in the present Action, Lackey et al. are silent with respect to sequencing the templates utilized therein to generate phosphorothioate oligonucleotides. In the absence of such teaching, the Examiner has failed to establish a nexus that substantiates the potential for an ordinarily skilled artisan to arrive at the alleged combination. The method of Lackey et al. is directed to methods of cleaving phosphorothioate oligonucleotides to generate relatively cleavage resistant phosphorothioate oligonucleotides having properties that facilitate their separation and purification after synthesis. There is, indeed, no reason to teach or suggest sequencing a template used for this purpose because the sequence of the template is already known. It is also, moreover, apparent that Lackey et al. do not teach resequencing any template. The Examiner has failed to address Applicant's previously asserted arguments directed to this point and is deferentially requested to do so. In short, no motivation can be discerned that would compel an ordinarily skilled practitioner to consider sequencing or resequencing a template of Lackey et al., because the sequence of the template is predetermined prior to synthesis of phosphorothioate oligonucleotides generated therefrom.

As for the Examiner's assertion that it would allegedly have been obvious to one of ordinary skill in the art to have modified the method of Balasubramanian et al. by removing the

complementary strand and resequencing the template as suggested by Lackey, Applicant retorts that there is no such teaching in Lackey. The Examiner is respectfully requested to identify any passages in Lackey to support the contention that this document teaches resequencing of any template. In the absence of such a passage, the Examiner's assertion is unsubstantiated and should be withdrawn. The Examiner's statement that one of skill in the art would allegedly have been motivated to remove the complementary strand and resequence the template for the benefit of verifying the results from the first sequencing reaction appears, moreover, to be attributable to hindsight reconstruction of the instant invention, rather than validating evidence. In light of the above, Applicant asserts that the teachings of Balasubramanian et al., Cheeseman, and Lackey et al. do not provide a teaching or suggestion directed to performing a first and second round of sequencing of the immobilised single-stranded template nucleic acid molecules and comparing the first and second rounds of sequencing of each immobilized single-stranded template nucleic acid molecule to confirm sequencing data, as called for in the amended claims. That being the case, the combined teachings of Balasubramanian et al., Cheeseman, and Lackey et al. fail to teach each and every element of the instant claims and, therefore, would not lead an ordinarily skilled practitioner to the presently claimed invention.

In view of the above arguments, the Examiner is respectfully requested to reconsider the validity of the rejection of claims 4, 27-29, and 30-31 under 35 U.S.C. §103 and withdraw the rejection.

Claim 32 is rejected under 35 USC § 103(a) as allegedly unpatentable over Balasubramanian et al. (WO 01/57248) as evidenced by Cheeseman (USPN 5,302,509) in view of Lackey et al. (USPN 5,652,126) as applied to claims 4 and 31 above and in further view of Barnes (WO 01/57249; published 8/2001). In view of the clarifying amendments to the claims and arguments presented herein, this rejection is respectfully traversed.

Regarding claim 32, which ultimately depends from claim 4, the deficiencies of the combined teachings of Balasubramanian et al., Cheeseman, and Lackey et al. with respect to the instant claims are described in detail above and are incorporated herein by reference in their

entireties. The teachings of Barnes fail to compensate for the aforementioned defects of Balasubramanian et al., Cheeseman, and Lackey et al. at least because Barnes does not provide the missing teaching or suggestion of performing a first and second round of sequencing of the immobilised single-stranded template nucleic acid molecules and comparing the first and second rounds of sequencing of each immobilized single-stranded template nucleic acid molecule to confirm sequencing data, as called for in the amended claims. In light of the above, these references in combination do not teach each and every element recited in claim 32 and, therefore, fail to render obvious the instant claims.

In view of the above, the Examiner is respectfully requested to reconsider and withdraw the rejection of claim 32 under 35 U.S.C. §103.

Fees

No additional fees are believed to be necessitated by this amendment. However, should this be an error, authorization is hereby given to charge Deposit Account No. 11-1153 for any underpayment or to credit any overpayment.

Conclusion

It is submitted, therefore, that the claims are in condition for allowance. No new matter has been introduced. Allowance of all claims at an early date is solicited. In the event that there are any questions concerning this amendment, or application in general, the Examiner is respectfully urged to telephone the undersigned so that prosecution of this application may be expedited.

Respectfully submitted,

Sarah J. Fashena

Sarah J. Fashena, PhD.
Agent for Applicant(s)
Registration No. 57,600

KLAUBER & JACKSON
411 Hackensack Avenue
Hackensack, New Jersey 07601
(201) 487-5800

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Enclosures: Substitute Sequence Listing [paper copy and computer readable format (CRF)];
Amendment directing entry of Substitute Sequence Listing into the record and statement supportive thereof